# The Current Landscape of Gliomatosis Cerebri & Changes in the WHO Classification

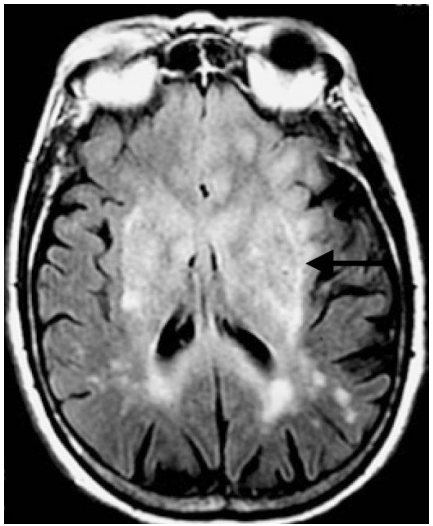
Surabhi Ranjan, MD
Clinical Fellow
Neuro-Oncology Branch
National Institutes of Health & Johns Hopkins University

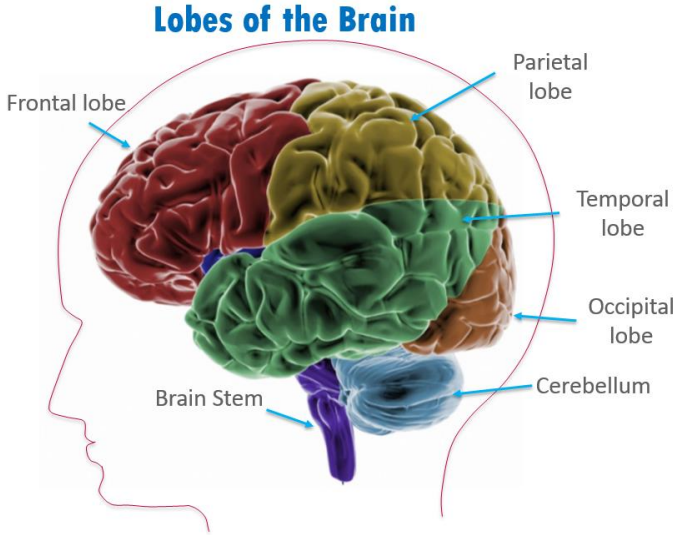

NATIONAL CANCER INSTITUTE
Center for Cancer Research

6/22/2017

# Gliomatosis Cerebri: Definition

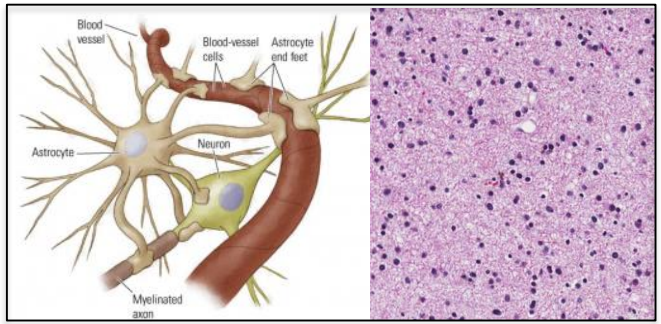
- A diffuse glioma (usually astrocytic) growth pattern consisting of exceptionally extensive infiltration of a large region of the CNS, with involvement of at least 3 cerebral lobes.
- Usually with bilateral involvement of cerebral hemisphere and/or deep grey matter, and frequent extension to brain stem, cerebellum and spinal cord.





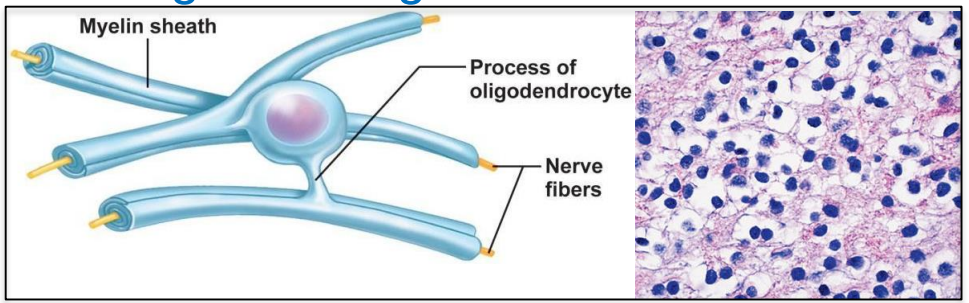
# Gliomas

## Astrocytic Tumors



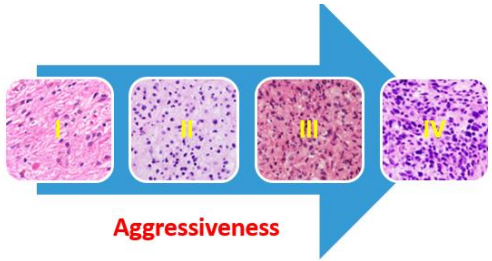

- Resemble astrocytes, which are the most numerous cells in the brain and provide metabolic and structural support to neurons
- Show TP53 mutation, ATRX mutation

## Oligodendroglial Tumors

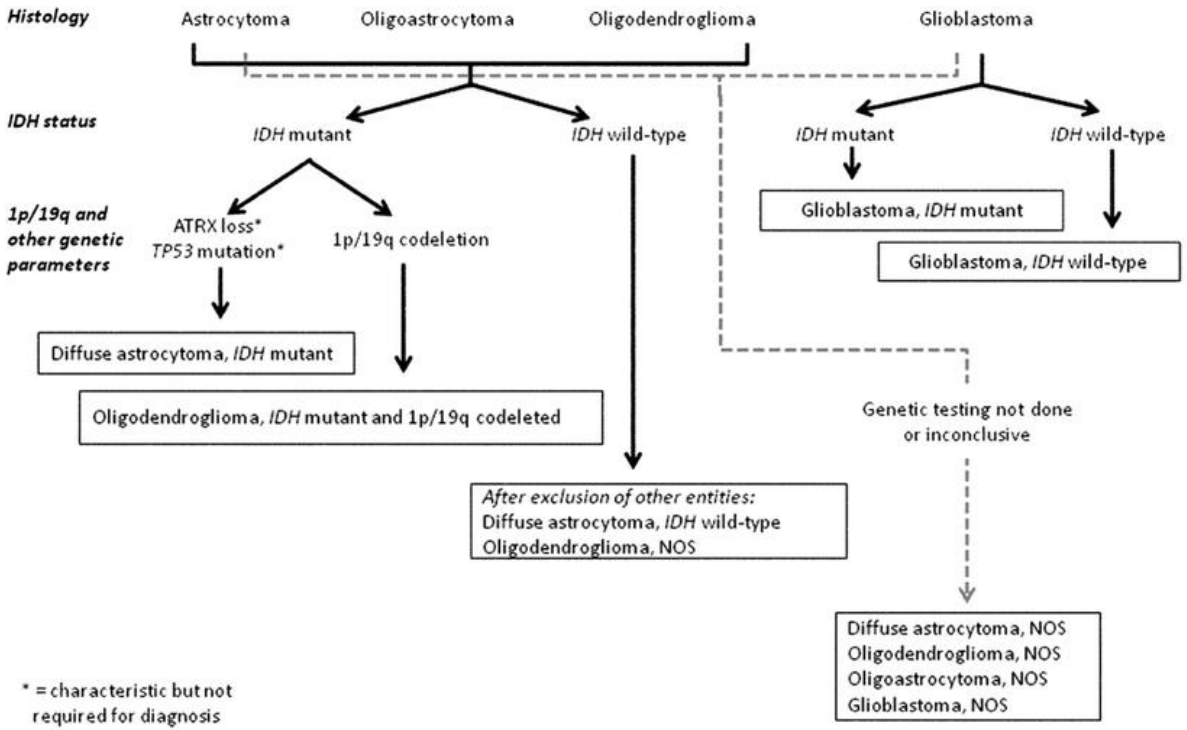



- Resemble oligodendroglia, which provide insulation and support to axons in the brain
- Show 1p/19q codeletion

## Tumor Grading



# Recent Changes in 2016 CNS WHO: Diffuse Gliomas




From: Louis DN et al. Acta Neuropathologica. 2016

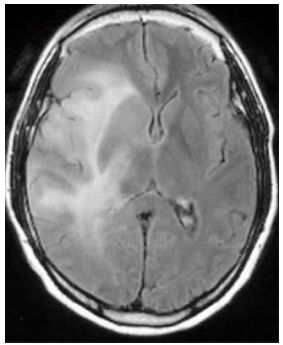
# Gliomatosis Cerebri: Classification

## Primary gliomatosis cerebri

- Arises spontaneously, without a prior history of brain tumor

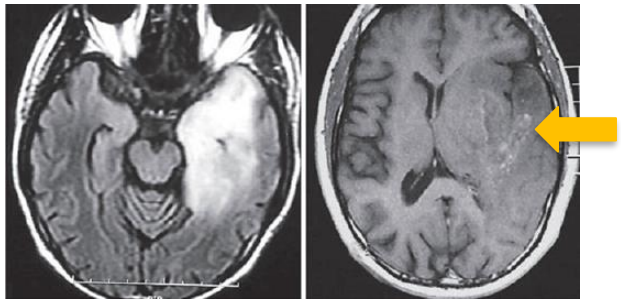
### Type I

- No obvious mass present



### Type II

- Diffuse infiltrative pattern + obvious tumor mass

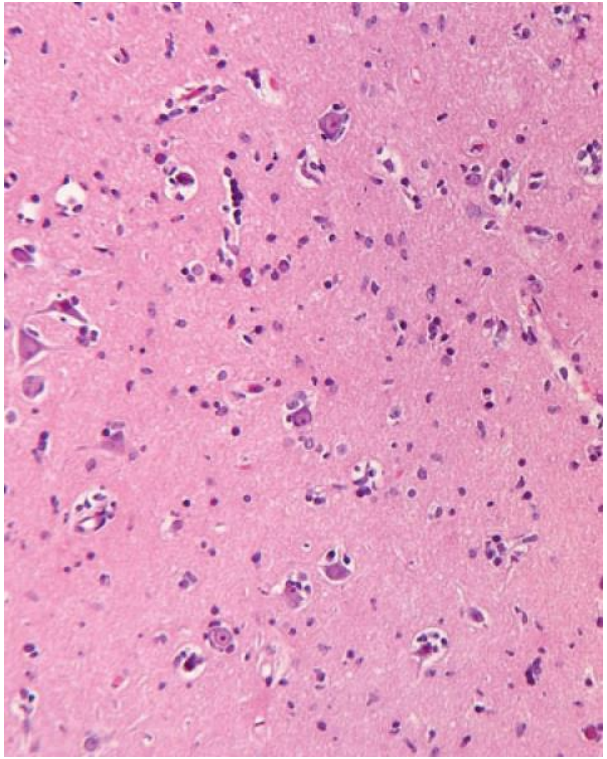


## Secondary gliomatosis cerebri

- Infiltrative spread of tumor cells from a previously diagnosed glioma
- Frequently associated with prior radiation or bevacizumab chemotherapy

# Histopathology

- Most gliomatosis cerebri are astrocytic tumors
- Rarely oligodendroglial or mixed
- Under the microscope, they can appear as grade II,III or IV glioma
- However, they behave like aggressive tumors and their behavior corresponds to grade III tumors
- Small, astrocytic cells with elongated nuclei
- Unlike typical grade III or IV tumor, new blood vessel formation, aggressive tumor cell division and necrosis are absent.



Gliomatosis cerebri: Grade II astrocytoma

# Epidemiology

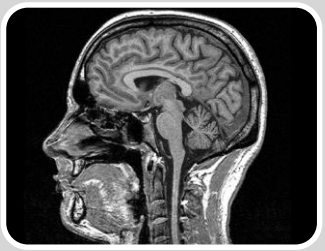
- All age groups (new born to 83 years)
- More common in adults
- Median age at diagnosis is 46 to 53 years
- Slight male predilection (1.4:1)

# Clinical Features

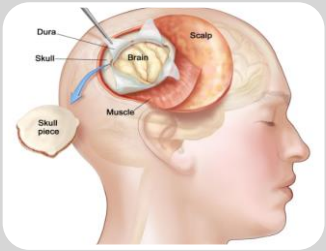
- Slowly progressing symptoms, which may delay diagnosis
- Limb weaknss
- Loss of sensation
- Seizure
- Progressive headache
- Memory loss
- A general feeling of being unwell

# Diagnosis

Neuro
-logical
exam

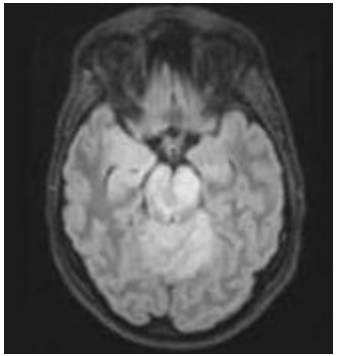


MRI of
the
Brain

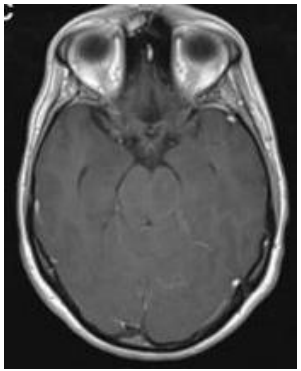



Tissue diagnosis (biopsy or partial resection)

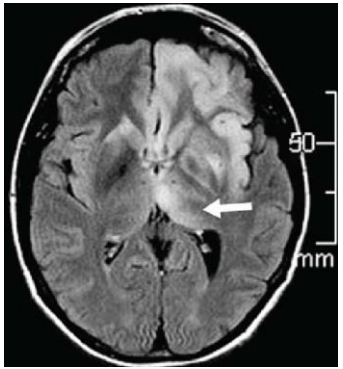
# MRI appearance



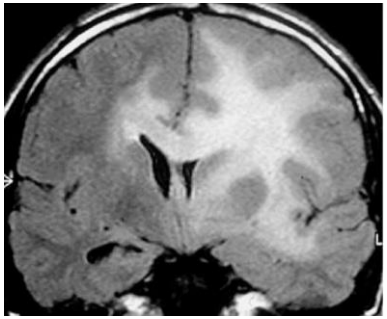
Diffuse hyperintensity on T2-FLAIR



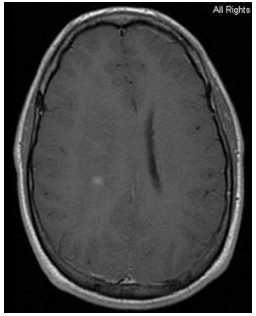
Hypo- or isointensity on T1




Diffuse infiltration of cortex and poor grey-white differentiation

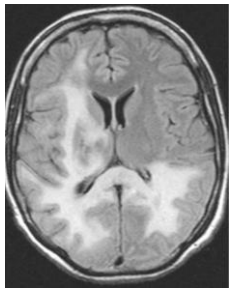


Thickening of gyri and enlargement of affected structures

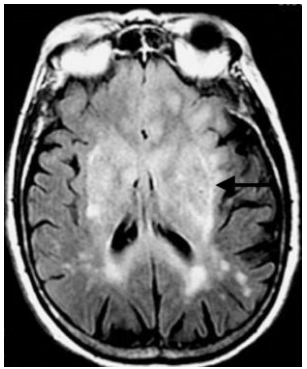


Patchy contrast-enhancement on T1

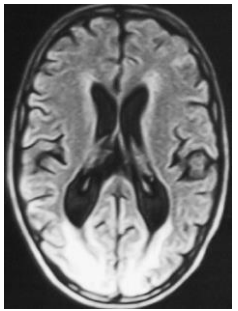
# Diseases which can look like Gliomatosis Cerebri



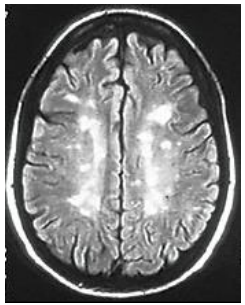
Progressive Multifocal Leukoencephalopathy



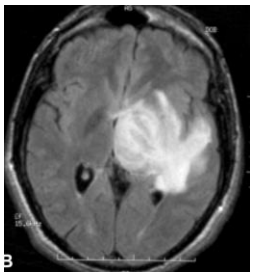
**Gliomatosis Cerebri**



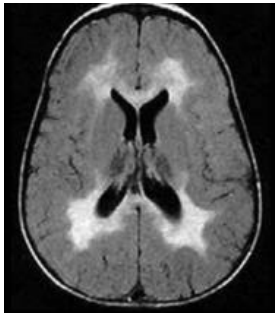
Subacute sclerosing panencephalitis



Multiple sclerosis

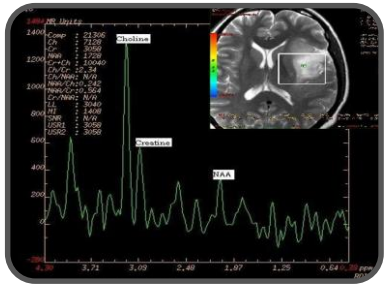


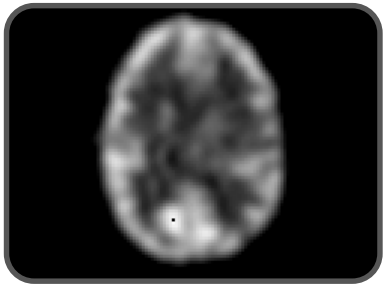
Behcet disease

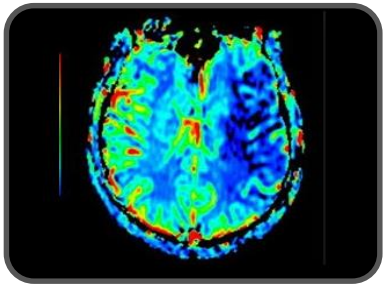


Leukodystrophy

# Advanced Imaging Techniques





## MRS

Choline/Creatine ratio ↑

NAA/Creatine ratio ↓

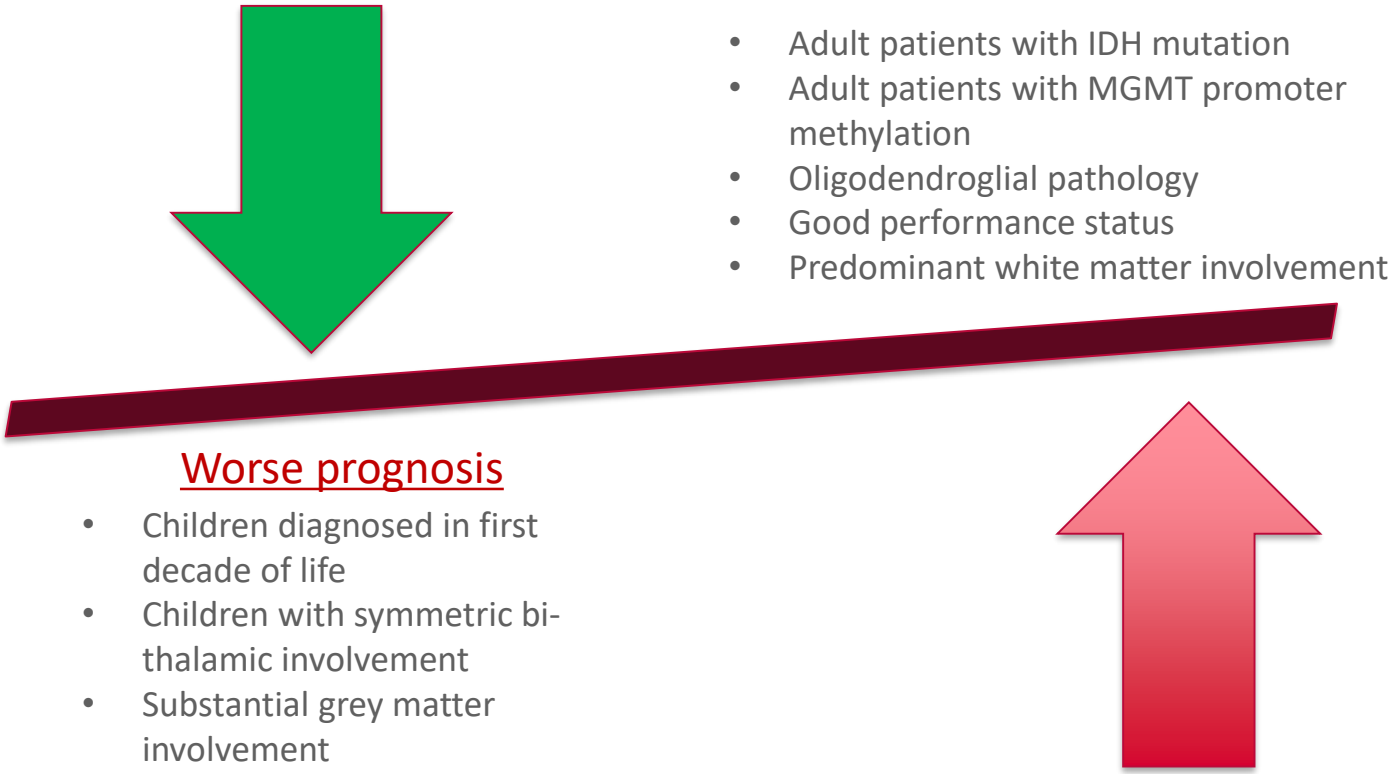
## FDG-PET

Usually ↓ glucose uptake

## MR Perfusion

lack of elevation of Cerebral Blood volume

# Factors affecting Patient Outcomes



## Good prognosis

- Adult patients with IDH mutation
- Adult patients with MGMT promoter methylation
- Oligodendroglial pathology
- Good performance status
- Predominant white matter involvement

## Worse prognosis

- Children diagnosed in first decade of life
- Children with symmetric bi-thalamic involvement
- Substantial grey matter involvement

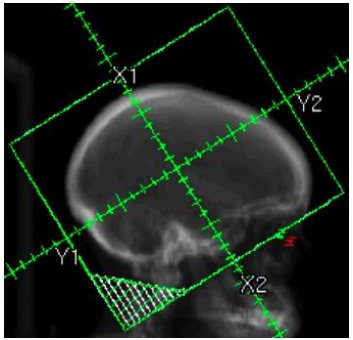
# Treatment: Role of Surgery

Establishing the diagnosis

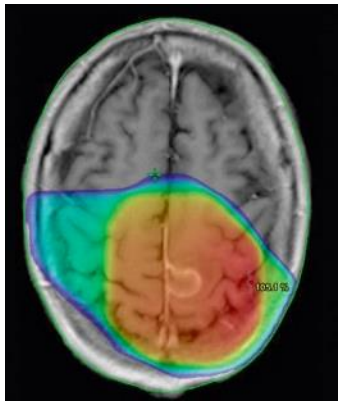
Partial resection can help in decreasing symptoms of brain swelling

Unclear if surgical debulking has a benefit in overall survival

# Treatment: Radiation Therapy




Whole-brain RT



Involved-field RT

- Role of radiation on overall survival is ambivalent.
- The role of radiation in children is unclear due to an absence of standard of care of treatment of pediatric high-grade gliomas and toxicity of the large field of RT.
- Four retrospective studies have reported a clinical response in 58% of patients and a radiographic response in 31% of patients (1-4).
- Another study found that patients who received radiation lived longer (27.5 months) as compared to 6.5 months without radiation therapy (5).
- A large retrospective study on 296 patients did not an overall survival benefit with radiation.

1.Elshaikh et al. Cancer. 2002
2. Cozad et al. Cancer. 1996
3. Perkins et al. nternational journal of radiation oncology, biology, physics. 2003
4. Kim et al. Acta neurochirurgica. 1998
5. Chen et al. Journal of Neiuro-Oncology. 2013
6. Taillibert et al. Journal of Neuro-Oncology. 2006

# Treatment: Chemotherapy

Ann Neurol. 2011 Sep;70(3):445-53. doi: 10.1002/ana.22478. Epub 2011 Jun 27.

**NOA-05 phase 2 trial of procarbazine and lomustine therapy in gliomatosis cerebri.**

Glas M[1], Bähr O, Felsberg J, Rasch K, Wiewrodt D, Schabet M, Simon M, Urbach H, Steinbach JP, Rieger J, Fimmers R, Bamberg M, Nägele T, Reifenberger G, Weller M, Herrlinger U; Neuro-Oncology Group of the German Cancer Society.

| | |
|---|---|
| NOA-05 | The only prospective clinical trial published to analyze the efficacy of primary chemotherapy in GC |
| | Phase II single arm study on 35 patients with GC |
| | Median progression free survival was 14 months and median overall survival was 30 months |

# Treatment: Chemotherapy

Neurology. 2004 Jul 27;63(2):270-5.

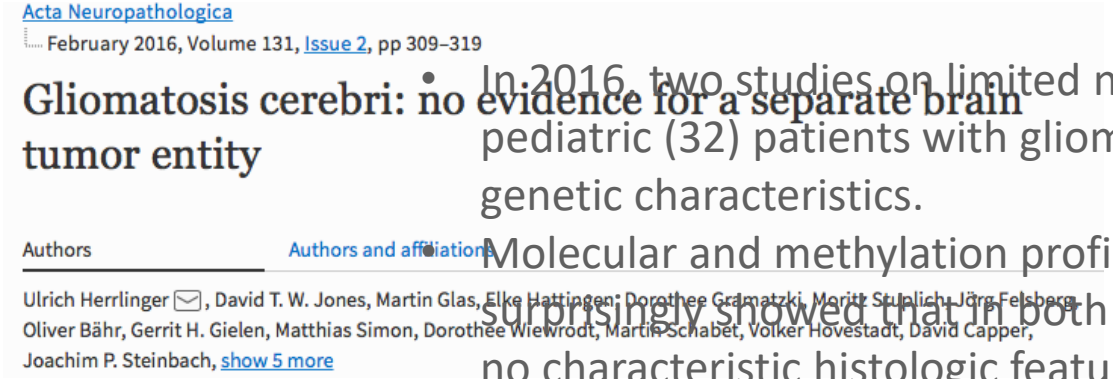
**Initial chemotherapy in gliomatosis cerebri.**

Sanson M[1], Cartalat-Carel S, Taillibert S, Napolitano M, Djafari L, Cougnard J, Gervais H, Laigle F, Carpentier A, Mokhtari K, Taillandier L, Chinot O, Duffau H, Honnorat J, Hoang-Xuan K, Delattre JY; ANOCEF group.

- Retrospectively compared response rate to procarbazine, vincristine and lomustine (PCV) versus temozolomide in a series of 63 patients with GC.
- No significant difference observed
- Other studies show that temozolomide can be used both as initial therapy or at the time of tumor progression.
- Gliomatosis cerebri with oligodendroglial pathology and 1p/19q codeletion have better response with temozolomide as compared to non-oligodendroglial GC.

**Randomized Phase II studies are needed to study the role of chemotherapy in Gliomatosis Cerebri.**

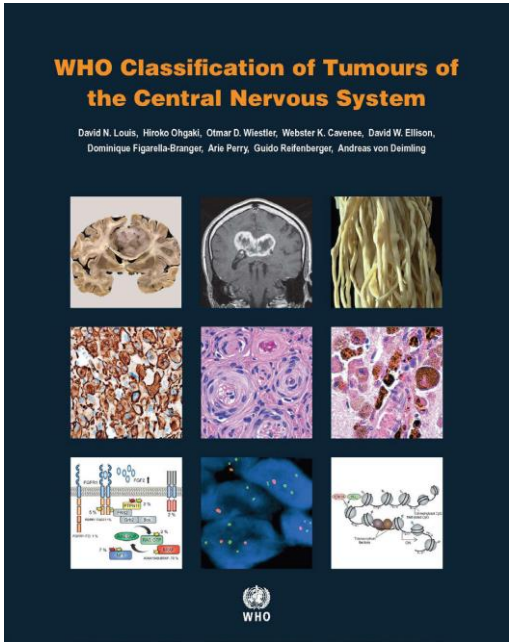
# Recent Molecular insights




- In 2016, two studies on limited number of adult (25) and pediatric (32) patients with gliomatosis cerebri explored its genetic characteristics.
- Molecular and methylation profiling in these studies surprisingly showed that in both adults and children, there are no characteristic histologic features or molecular subgroups exclusive to the diagnosis of gliomatosis cerebri


- Led to deletion of gliomatosis cerebri as a separate pathologic entity in the 2016 WHO classification of CNS tumors

# WHO classification of Tumors of the Central Nervous System 2016




- Strives to incorporate what is current and established in the field of neuro-oncology, rather to direct the “latest and greatest” of future neuro-oncology endeavors

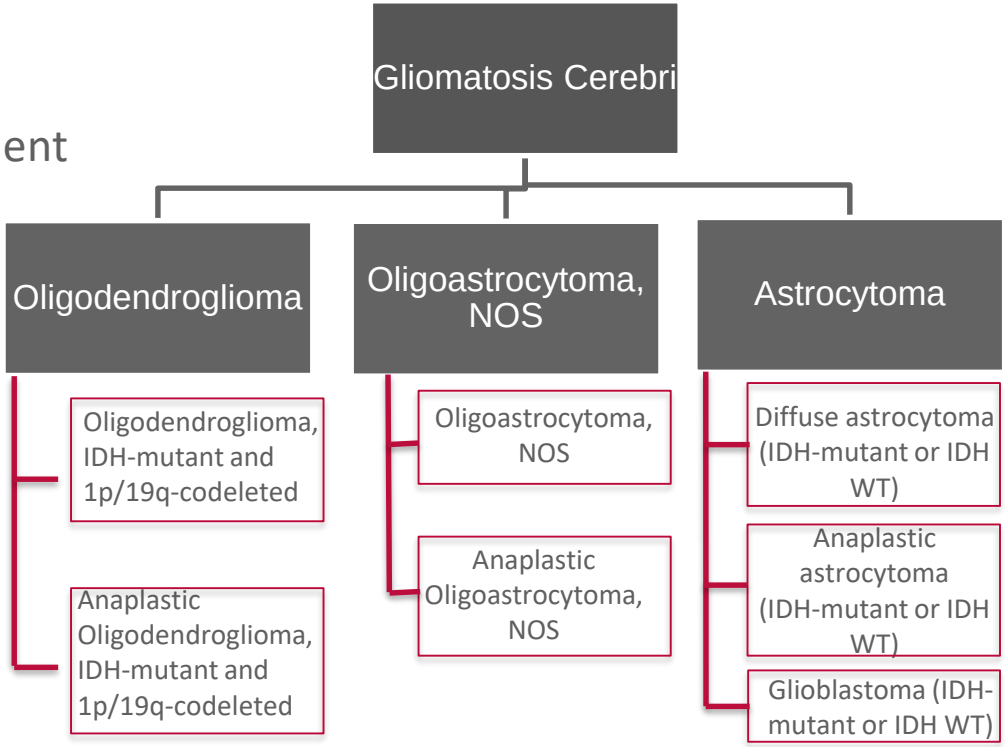
- Seminal shift from the concept of classification of tumors according to their microscopic similaries and level of differentiation,  to the current classification based on the genetic basis of tumor formation

# Major Changes in 2016 CNS WHO: Deleted entities & variants

- Gliomatosis cerebri
- Diffuse intrinsic po[illegible] glioma
- Glioblastoma with [illegible]al component
- Protoplasmi[illegible]rocytoma variants
- Ce[illegible]dymoma variant
- Primitive neuroectodermal tumor

# Gliomatosis Cerebri in 2016 CNS WHO Classification

- Not a distinct pathological disease
- Now considered to be a pattern of exceptionally widespread involvement of brain by tumor cells
- Can be seen in any of the diffuse glioma subtypes

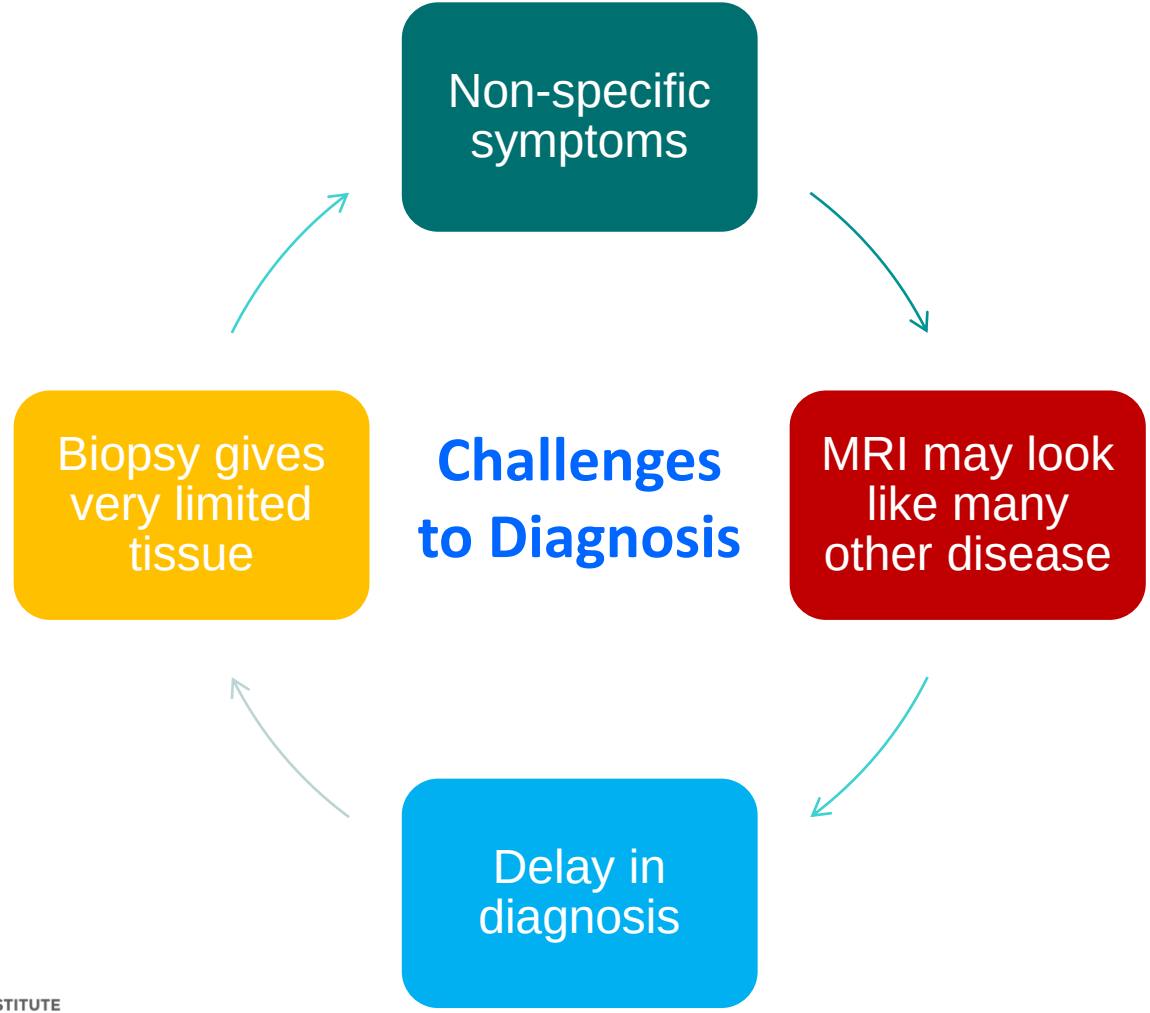


# Why is Gliomatosis Cerebri a unique disease? The need for recognition as a clinical disease entity?

# Prognosis of patients with gliomatosis cerebri vs diffuse gliomas

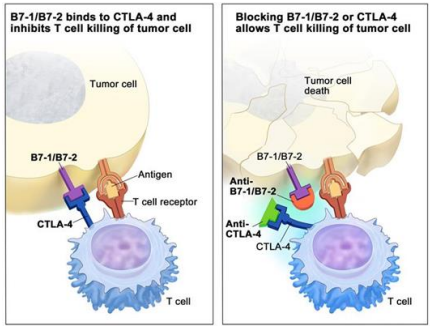
**Patient survival**

| Grade | Gliomatosis Cerebri | Diffuse gliomas |
|---|---|---|
| II | 18 to 35 months | 8 to 13 years |
| III | 12 to 29 months | 37 months to 15 years |
| IV | 9 to 36 months | 15 to 16 months |


Non-specific symptoms
MRI may look like many other disease
Delay in diagnosis
Biopsy gives very limited tissue
Challenges to Diagnosis


Biology behind extreme invasiveness still unknown
Advanced symptoms and large tumor limit treatment options
No randomized controlled trials for GC
Unclear if different subtypes of GC should be treated with different regimens
Unclear if pediatric and adult GC should be treated differently
Large field RT or whole brain RT has significant impact on QoL
Challenges in Treatment

# New Avenues for progress

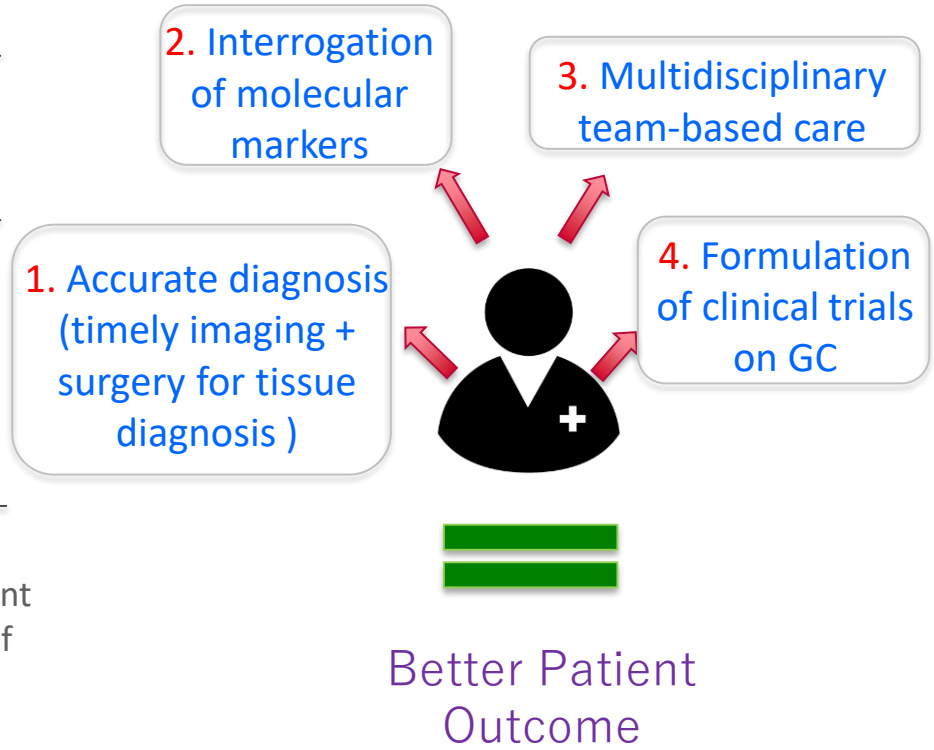



Source:www.cancer.gov

- Formation of a Gliomatosis Cerebri Registry to study the natural history and genetic characteristics
- Development of immunotherapy trials for Gliomatosis Cerebri
- Role of IDH inhibitors – 17 to 48% patients with GC have IDH mutation
- VEGF and COX2 expression in Gliomatosis Cerebri: role of drugs such as celecoxib
- Following patients with advanced imaging such as MRS, PET and MR perfusion

# Conclusions

- Gliomatosis cerebri is a rare disease with great pathological and clinical heterogeneity
- Recent molecular studies have shown no distinct features in adult or pediatric gliomatosis cerebri as compared to diffuse gliomas
- However the biology behind the extreme invasiveness of disease is unknown
- Patient with gliomatosis cerebri do much worse than patients with diffuse gliomas of corresponding grades
- We now have advanced imaging and genetic studies such as DNA, RNA and protein sequencing and the establishment of a GC Registry. to study gliomatosis cerebri as avenues of progress.



# Acknowledgment

National Institutes of Health
Dr. Kathy Warren

# THANK YOU



NATIONAL CANCER INSTITUTE
Center for Cancer Research

www.cancer.gov

www.cancer.gov/espanol